BRACAnalysis CDx™, Tumor BRACAnalysis CDx™, myChoice HRD™ - A portfolio of Companion Diagnostic Products to optimize therapeutic selection for cancer patients

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Executive VP Emerging Products
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NMBio
Aug 11
Agenda

• Introduction (this slide)

• A Myriad CDx Story
  – Brief story of 3 Myriad CDx products: BRACAnalysis CDx, tumor BRACAnalysis CDx, myChoice HRD
  – Why
    ▪ Not your typical CDx story, but a good CDx story, and maybe the best sort of CDx for Dx Company
    ▪ Unique portfolio story
    ▪ Topical: CDx, Regulatory, Pharma -Dx Partnerships
  – Stop me at anytime with General Questions on any related topic

• Discussion
Myriad’s Vision (but a moment on Myriad’s Past)

Answering Patient’s Most Pressing Questions: 4 in 6 Strategy

- Oncology
- Preventive Care
- Urology
- Autoimmune
- Dermatology
- Neuroscience
Companion Diagnostic Partnerships

Leader in Companion Diagnostics
- Approximately 20 pharmaceutical partners

Complete Biomarker Capability
- DNA, RNA and Protein

Major PARP Inhibitor Opportunity
- Collaboration with 5 pharmaceutical companies

Diverse Disease Indications
- Cancer
- Depression
- Diabetes
- Autoimmune Disease
Myriad’s PARPi and Platinum CDx Program

PARP Inhibitors:
• Collaborations with five pharma partners
• Supporting 13 Phase 3 world-wide clinical trials
• Current indications include breast, ovarian and prostate cancer

Platinum Drugs:
• Guide treatment decisions for neoadjuvant, adjuvant and metastatic triple negative breast cancer
• All indications represent potential market of over one million patients
The Unique Evolution of “CLIA” BRACAnalysis

The History (simplified)

• Clinical, CLIA-LDT Hereditary Cancer Testing for BRCA1 & BRCA2 mutations
• Farmer et al, Nature 2005
• Jan 2011, negative top-line results for iniparib disclosed by Sanofi
• Dec 2011 - AZ halts development of olaparib in ovarian cancer
• 2013 Myriad – AZ enter into a CDx Co-development agreement
• Dec 19, 2014 FDA Approves Lynparza™ and BRACAnalysis CDx™

The Present

All Cancer Patients
myChoice HRD
Tumor BRACAnalysis CDx
BRACAnalysis CDx

Myriad Genetics, Inc.
Why are PARPi’s Effective in *BRCA* Deficient Cells?

polyADP ribose polymerase (PARP) and *BRCA* both function to repair DNA
polyADP ribose polymerase (PARP) and BRCA both function to repair DNA

Tumors with BRCA mutations already have a DNA repair defect
BRCA Mutations and PARPi’s Cause Cell Death Due to Accumulation of DNA Damage

polyADP ribose polymerase (PARP) and BRCA both function to repair DNA

Tumors with BRCA mutations already have a DNA repair defect

Inhibiting PARP in BRCA deficient cells prevents the cell from replicating- effectively killing the cancer cells
Patients with gBRCA Mutation Respond to Olaparib

Olaparib maintenance in Recurrent Platinum Sensitive Ovarian Cancer

ASCO 2013 & Lederman et al, Lancet Onc 2014
Subset of Patients w/o gBRCA Mutations Respond to Olaparib

Can we identify those patients who are gBRCA1/2 wt and are responsive

ASCO 2013 & Lederman et al, Lancet Onc 2014
**Somatic Mutations ID Some of the “Missing” Responders**

- **Germline (hereditary) mutations** exist in the patient’s germ cells and thus can be passed on to future generations.

- **Somatic (acquired) mutations** can spontaneously arise in any cell in the body (except germ cells) at any time during the patient’s life.
A companion diagnostic for Ovarian Cancer

Guides the selection of patients for select PARP inhibitor therapy
## Tumor BRACAnalysis CDx

20 years of BRACAnalysis experience applied to testing FFPE tumor tissue

<table>
<thead>
<tr>
<th>&gt;99% test specificity and sensitivity</th>
<th>&gt;97% variant classification for BRCA1/BRCA2 mutations</th>
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<tbody>
<tr>
<td>Ensuring accurate identification of those patients who could benefit from targeted treatment</td>
<td>Increasing certainty for patients and ensuring more patients have a clearer management pathway</td>
</tr>
<tr>
<td><strong>Average 14-day laboratory turnaround time</strong></td>
<td><strong>CE marking</strong></td>
</tr>
<tr>
<td>Timely reporting ensuring results are available to support clinical decisions</td>
<td>Verifying that Tumor BRACAnalysis, complies with all requirements of the European Directive for performance and safety</td>
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Available as a CE marked product in Myriad Munich Laboratory
Subset of Patients w/o gBRCA Mutations Respond to Olaparib

Can we identify those patients who are gBRCA1/2 *wt* and are responsive

ASCION 2013 & Lederman et al, Lancet Onc 2014
Myriad’s HRD Assay Development Approach

**Develop a DNA-based assay capable of detecting Homologous Recombination Deficiency (HRD) regardless of its etiology or mechanism**

- No need to know all kinds of causal alterations in all relevant genes
- HR deficiency footprint should be the same in all cancer
- HR Deficiency status includes all known functional BRCA defects and captures “beyond BRCA” HR deficiencies
Calculation of the HRD Score

- **LOH Score**: The number of LOH regions longer than 15 Mb but shorter than the length of a whole chromosome.
- **TAI Score**: The number of regions with allelic imbalance which extend to the subtelomere but do not cross the centromere (Birkbak et al, Cancer Discovery 2012).
- **LST Score**: The number of chromosomal breaks between adjacent regions longer than 10 Mb after filtering out regions shorter than 3 Mb (Popova et al, Cancer Research 2012).

"HRD Score" = TAI Score + LOH Score + LST Score
HRD Score Distribution

**Combined studies**
*breast and ovarian*

- **Intact**
  - 5th pctl 2
  - Min 0
  - 1st Qu 12
  - Median 22
  - Mean 25.24
  - 3rd Qu 34
  - Max 89

- **Deficient**
  - 5th pctl 42
  - Min 11
  - 1st Qu 55
  - Median 64
  - Mean 62.58
  - 3rd Qu 70
  - Max 96

**BRCA intact n = 790**
**BRCA deficient n = 268**

**LOW HRD:** 0 to 41
**HIGH HRD:** 42 to 100
myChoice HRD Rearrangements

Figure 4:

Figure 5:

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<tr>
<th>HRD</th>
<th>NTAi</th>
<th>LST</th>
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<td>1</td>
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HRD applied to PDX models of TNBC and Ovarian Cancer

Wilcoxen et al. ASCO 2015
myChoice HRD Predicts Response to Platinum Regimes

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Description</th>
<th>Overall Response</th>
<th>Response to platinum in HR deficient/non-def</th>
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<tr>
<td>PrECOG 0105</td>
<td>Single arm</td>
<td>36%</td>
<td>41%/10%</td>
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<tr>
<td></td>
<td>Gem/Carbo/Iniparib</td>
<td></td>
<td>RCB 0/1</td>
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<tr>
<td></td>
<td>93 patients</td>
<td></td>
<td></td>
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<tr>
<td>NCT01372579</td>
<td>Single arm</td>
<td>42%</td>
<td>75%/14%</td>
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<tr>
<td></td>
<td>Carbo/eribulin</td>
<td></td>
<td>pCR</td>
</tr>
<tr>
<td>NCT00148694</td>
<td>Two Phase II studies</td>
<td>15%</td>
<td>28%/0%</td>
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<tr>
<td>/NCT00580333</td>
<td>Cisplatin</td>
<td></td>
<td>pCR</td>
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<tr>
<td></td>
<td>Cisplatin+/- bevacizumab</td>
<td>21%</td>
<td></td>
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<tr>
<td>GeparSixto</td>
<td>Randomized phase 2</td>
<td>53%</td>
<td>64%/30% carboplat</td>
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<tr>
<td></td>
<td>Doxil/paclitaxel</td>
<td></td>
<td>34%/20% no carboplat</td>
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<tr>
<td></td>
<td>bevacizumab (PM) vs PM + carbo</td>
<td></td>
<td>pCR ypT0/ypN0 endpoint</td>
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3 FDA-Approved CDx Tests: Complete Franchise

- **BRACAnalysis CDx™:** an in vitro diagnostic device intended [...] to aid in identifying ovarian cancer patients [...] eligible for treatment with Lynparza™ (olaparib).

- **Tumor BRACAnalysis CDx™:** an in vitro diagnostic [...] using genomic deoxyribonucleic acid (DNA) extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. Results of the test may be used as an aid in treatment decision making for poly ADP ribose polymerase (PARP) inhibitors [...].

- **myChoice HRD™:** TBD – but probably very similar
Companion Diagnostic Portfolio

- Identify cancer patients with tumors that lack the ability to repair DNA
- Likely to respond to DNA damaging agents (PARP or platinum drugs)

Ovarian Cancer Patients Testing Positive

- 14%
- 22%
- 48%
Myriad’s Vision

Answering Patient’s Most Pressing Questions

- Oncology
- Preventive Care
- Urology
- Autoimmune
- Dermatology
- Neuroscience

With What?
Will I?
Should I?
Do I?